IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Friede et al.	Group Art Unit: 1648
Filed: 28 March 2001	Examiner: Z. Lucas
Serial No.: 09/819,464	Atty Reference: B45070 US1
For: Vaccines	Date: 18 January 2010

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This Reply Brief is filed pursuant to the "Examiner's Answer" filed November 19, 2009.

STATUS OF CLAIMS

Claims 74-84, 94 and 95 are pending in this application. The final rejection of Claims 74-84, 94 and 95 as obvious is appealed.

The application was originally filed with claims 1-49. In response to a restriction requirement, Appellants elected method claims 47 and 48 and later added new dependent claims 50-73. Claims 1-46 and 49 were withdrawn being drawn to non-elected inventions. All the original claims were later canceled and replaced with new composition claims 74-84 and with new method claims 85-93, dependent upon the composition claims. In response to a second restriction requirement, Claims 74-84 were elected, and the non-elected method claims were withdrawn and later canceled. In subsequent response, a new dependent claim 94 was added. Finally dependent claim 95 and a new independent method claim 96 was added; claim 96 was later canceled, leaving claims 74-84, 94 and 95 pending.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 74-76, 78, 80, 82-84, 94 and 95 have been rejected by the Examiner under 35 U.S.C. §103 as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (U.S Pat No. 5,583,112) and further by routine optimization.

II. Claims 77, 79 and 81 have been rejected by the Examiner under 35 U.S.C. §103(a) as being unpatentable over Lipford (Vaccine 12:72-80) in view of the teachings of Kensil (5,583,112) and further in view of Prieels et al. (WO94/00153) and further by routine optimization.

ARGUMENT

As to the first and second grounds for rejection listed above, Appellants assert in the Appeal Brief that one of ordinary skill in the art would not have been motivated to combine QS21 as disclosed in Kensil with the Quil A/sterol composition disclosed in Lipford and more particularly, would not have been motivated to combine these elements as set forth in the Appellants' claims. (Page 10.) Appellants support this assertion with three arguments. First Appellants argue that the art does not suggest an apparent reason to combine the disclosed elements, that is, the references do not suggest (i) a motivation to combine QS21 in a sterol composition or (ii) a motivation to substitute QS21 for Quil A in Lipford's compositions. Second Appellants argue that there is no motivation in the references to combine the elements disclosed in the prior art in the claimed fashion, or more specifically, there is no motivation to combine QS21 with Lipford's sterol compositions in the ratios of saponin to sterol claimed by the Appellants. Third, Appellants argue that the ratio of saponin to sterol was not recognized as a result-effective parameter in the art, and therefore it is not obvious to optimize the sterol to saponin ratio in the compositions disclosed or suggested by the cited references.

In his Answer the Examiner has addressed each of these three arguments. The Examiner has not found the first argument to be persuasive and has argued the rejection be maintained. The Examiner found the second argument to be persuasive in part, i.e. persuasive with respect to the limitation of the claimed ratios not being obvious in light of the cited references alone. The

Examiner has not found the third argument persuasive and has argued the rejection be maintained. Appellants now reply to the assertions and arguments presented in the Examiner's Answer.

A. The art does not suggest an apparent reason to combine the disclosed elements.

(i) References provide no motivation to use QS21 in a sterol composition

In the Appeal Brief, Appellants presented evidence and argument to show that one of skill in the art would not have a reason to combine QS21 with cholesterol principally because the severe necrosis caused by the use of QS21 alone, as observed by Appellants and disclosed in the present application, was not known in the art. (Brief pages 7-8.). In his answer, the Examiner explained that the Examiner does not have to rely on the same motivation as the Appellant to show a motivation to combine various teachings, where some other motivation for combining the various teachings can be shown (Answer page 10 first paragraph.) The Examiner agrees that the prior art does not recognize the necrosis referred to by the Appellant, but asserts that the motivation to combine is based upon on (a) Kensil's teaching that QS21 induces hemolysis, and (b) Lipford's statement "that the hemolytic quality of Quil A appears to be due at least in part to its ability to intercalate with cholesterol-containing membranes." (Answer page 10, citing Lipford page 78.) Relying on these disclosures, the Examiner concludes that a person of ordinary skill in the art would be motivated to combine QS21 and sterol "to reduce its hemolytic effects." (Answer page 10, second paragraph.)

While it is true that Lipford and Kensil recognize the hemolytic qualities of the saponins, Appellants respectfully disagree with the Examiner's conclusion. Kensil does not teach or suggest a need to reduce the hemolytic effects of QS21. Nor does Kensil suggest that adding a sterol to QS21 could result in such a reduction. Likewise, Lipford does not teach or suggest a need to reduce the hemolytic qualities of the Quil A liposomes (in fact, Lipford teaches the opposite – see below). Nor does Lipford comment on the effect of cholesterol on the hemolytic qualities of Quil A liposomes. Lipford does not indicate that including a sterol in Quil A liposomes can decrease the hemolytic qualities of the saponins contained therein; therefore Lipford does not provide motivation to combine QS21 with sterol. The Examiner's rejection combines a supposition concerning saponin and sterol interactions with an assumption (which is incorrect – see below) that the references disclose a need to reduce the hemolysis induced by QS21. Suppositions and assumptions of course do not provide sufficient rationale to support a conclusion of obviousness.

As part of his reasoning for the rejection, the Examiner has argued that Lipford provides a motivation to reduce hemolysis, however Appellants submit that Lipford indicates just the opposite. As the Examiner pointed out in his Answer, the Lipford reference discloses Quil A-containing liposomes as an alternative to Quil A- containing immunostimulating complexes (ISCOMS). Lipford hoped the Quil A liposome would retain particular properties of Quil A

ISCOMS, while overcoming undesired properties that limit the use of ISCOMs. (Answer page 4.) In the Discussion section of the Lipford paper, the author states that in his approach to making Quil-A liposomes, he "aimed to preserve the qualities of ISCOMs which allow [CD8+ cytolytic T-cell] induction." (Page 78, column 1, last paragraph, emphasis added.) Lipford explains,

> "Two aspects of ISCOMs are considered important to their action: liposome structure and the adjuvant qualities of Quil A. . . . It has been shown that liposomes constructed in such a way as to be fusogenic at reduced pH can shuttle ovalbumin into the MHC Class I pathway. ….. This fusion event results in the liposome dumping its contents into the cytosol of the cell. Quil A may be responsible for a similar phenomenon in Quil A-containing liposomes. Quil A can be haemolytic, a quality explained by its hydrophobic properties and its ability to intercalate with cholesterol-containing membranes. It has been proposed that ISCOMs transport antigen into the cytosolic compartment by membrane-fusogenic properties conferred by Quil A." (Lipford page 78, first column, emphasis added.)

Therefore, rather than directing the skilled person to attempt to reduce hemolysis as the Examiner contends, Lipford sees advantages in the property when liposomes are used to carry antigen. Hemolysis is thus one of the "adjuvant qualities" of Quil A that Lipford hoped to preserve in the Quil A liposomes and is not a quality Lipford wanted to reduce, as suggested by the Examiner.

Kensil teaches that QS21 is "well tolerated" when injected in mice (column 27 lines 11 –

17) and is silent with respect to any need to reduce hemolysis. A skilled person, wishing to use QS21 as a vaccine adjuvant would, upon reading Kensil, be motivated to use it in the aqueous form, which is taught by Kensil to be well tolerated. Accordingly, applicants submit that Kensil does not provide motivation to formulate QS21 as presently claimed. Given that Kensil teaches that QS21 in aqueous form has an adjuvant effect and is well tolerated, Kensil does not provide a skilled person with any need or motivation to look for more complicated ways to formulate it. The present inventors have formulated QS21 in sterol containing liposomes because of their recognition of the problem of necrosis at the injection site. Kensil does not recognize this problem or indeed any problem with aqueous QS21 and therefore provides no motivation to the skilled person to reduce hemolysis by formulating QS21 in sterol containing liposomes.

Neither Kensil nor Lipford suggest a need to reduce the hemolytic properties of QS21 but rather teach away from such a combination. Even if, *arguendo,* such a need to reduce hemolysis were disclosed, neither reference discloses a means by which one of ordinary skill in the art could reduce the hemolytic properties of QS21. The Examiner's argument that one of ordinary skill in the art would be motivated to combine the references in order to reduce hemolysis is not supported by the art and therefore Appellants submit that the Examiner has not made prima facie showing of obviousness.

ii. References do not motivate substituting QS21 for Quil A in Lipford's composition

The Examiner's argument that the purified QS21 taught in the Kensil reference is an

obvious substitute for Quil A compositions of Lipford relies on three statements which the Examiner contends are supported by the cited references:

(1) QS21 has adjuvant effects equal to or greater than Quil A,

(2) purified saponins show adjuvant effects at lower doses than crude saponin extracts and

(3) purified saponins are less toxic (hemolytic) than the Quil A extract. (Brief, page 5.)

Appellants argued these statements are not supported by the Kensil reference. With respect to statement (1), Appellants point out that the Kensil reference provides no showing that QS21 has greater adjuvant effects than Quil A. (Brief page 8.) With respect to statements (2) and (3), Appellants argue that generalized statements regarding "purified saponins" could not inform one of skill in the art sufficiently to motivate the use of QS21 as a substitute for Quil A" (Brief page 9.) In particular, with respect to statement (3) Appellants submit that statement (3) "while possibly accurate as applied to some of Kensil's purified saponins, is only partially accurate as applied to QS21." (Brief page 9.)

In support of statement (1), the Examiner has answered saying that Kensil shows QS21 has adjuvant effects at lower dosages than crude extracts (i.e. Quil A) and therefore concludes that QS21 has greater adjuvant effect. Appellants maintain the traversal and submit that a showing of adjuvant effects at *lower* dosages (increased potency) does not equate to a showing

of greater overall adjuvant effects (increased efficacy). There is no showing that QS21 could achieve a greater adjuvant effect than Quil A. There is no comparison of dose-response curves for Quil A and QS21. Dose-response curves for QS21's ability to boost IgG titers are shown (see e.g., Figure 15), but are not compared to Quil A to show increased efficacy. Increased potency does not, by itself, establish that a compound can achieve a greater maximum effect.

As to statement (2) in light of the Examiner's Answer, Appellants concede Examiner's point. Kensil does suggest that purified saponins (including QS21) give equal adjuvant effect at lower doses than crude saponins (including Quil A).

In support of statement (3) regarding purified saponins having lower toxicity/hemolysis, the Examiner has answered, stating that "the conclusions of the reference are based on data presented in the reference which indicate that QS21 shows reduced toxicity relative to Quil A, albeit maybe not as significant a reduction as other purified fractions. " The Examiner refers to Figure 12 which shows hemolysis caused by selected fractions and Quil A. Contrary to the Examiner's assertion, Kensil does not conclude that there is a significant difference in the hemolytic activity of QS21 compared to that of Quil A. Rather, referencing the data in Figure 12, Kensil notes that "QA-17, QA-18, QA-21 ["QS21"], and Superlos 'Quil A' caused partial hemolysis at concentrations as low as 25 ug/ml whereas partial hemolysis was observed with QA-8 at 150 ug/ml. No hemolysis was observed with QA-7 at the concentration tested." Col 20

lines 36-41. Thus, Kensil groups QA21 and Quil A together, describing them as causing "partial hemolysis" at the same dosage; Kensil does not teach or suggest that hemolysis of QS21 is significantly different than that of Quil A.

Additionally the Examiner argues that even if QS21 is only marginally less toxic than Quil A, QS21 can be administered at lower doses which would offset toxicity relative to Quil A. This requires an assumption that toxicity reliably decreases as the dose is decreased. As with statement (1) Appellants again maintain that just as an adjuvant's potency cannot automatically be equated with efficacy, neither can potency be equated with toxicity, without further study on the specific compounds at issue.

The Examiner has maintained that it would be obvious to those of ordinary skill in the art to substitute the purified saponins of Kensil, one of which is QS-21, for the crude Quil A extract used in Lipford and moreover, the Examiner asserts that one of ordinary skill would be able to do so with a reasonable expectation of success. The Examiner suggests a reasonable expectation of success can be based on Lipford's statement that "two aspects of ISCOMs are considered important to their action: liposome structure and the adjuvant qualities of Quil A" and that Kensil indicates the properties of Quil A "are also indicative of saponins in general" and thus QS21 "would have these properties." (Answer page 5, first paragraph.)

Appellants respectfully disagree. Since the aim of Lipford's study is to make 'ISCOM-like', Quil A liposomes, and both the "liposomal structure" and "adjuvant qualities" are important to ISCOM action, one could not have a reasonable expectation of successfully substituting QS21 for Quil A in the Lipford composition. While Quil A and QS21 may have some similarities, they are not the same. Kensil teaches that "the common properties of saponins are not reflected in common chemical composition." Col 1 lines 45-46. Kensil also explains that Quil A, which is isolated from the bark of the South American tree *Quillaja saponaria* Molina, "is characterized chemically as a carbohydrate moiety in glycosidic linkage to the triterpenoid quillaic acid" and shows "considerable heterogeneity." (Kensil Col 2 lines 1-2; see also Figures 3A-B). Obviously purified QS21, which is only one fraction of Quil A does not have Quil A's composition or share its degree of heterogeneity. Kensil reported that QS21 was well tolerated when injected in mice as compared to Quil A. Column 27 lines 11-17. Thus, even if *arguendo* a person of ordinary skill in the art were motivated to substitute QS21 for the Quil A in a Lipford composition, given the differences in composition and activity between Quil A and QS21 disclosed by Kensil, one of skill in the art could not reasonably expect a QS21-substituted liposome to maintain the "liposome structure and Quil A adjuvant qualities" that Lipford notes are important for preserving ISCOM-like activity in his liposomes.

Lastly, the Examiner argues that "regardless of the teachings of Kensil regarding the operability of QS21 in comparison to Quil A, the reference does indicate the compound has

"adjuvant activity" and therefore is the functional equivalent of Quil A, making it prima facie obvious to substitute one for the other." (Answer page 13 citing MPEP 2144.06.) Appellants submit that the Examiner's rejection is not well taken. The fact that two compositions are recognized in the art to have adjuvant activity does not render them substitutable equivalents. There are numerous and diverse compounds and compositions which exhibit adjuvant activity and one cannot reasonably conclude that they are all equivalents because they are all immunogenic. As stated in the MPEP 2144.06, "[in] order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on . . . the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958.)" As explained in the paragraph above, Kensil does not recognize QS21 and Quil A as equivalents.

B. There is no motivation to combine the elements in the fashion claimed.

As previously explained, the Examiner found Appellants' second argument to be persuasive with respect to the limitation of the claimed ratios being obvious in light of the cited references alone. Claims 74-76, 78, 80, 82-84, 94 were not allowed, however. The Examiner has modified the basis of the rejection to include both the cited references and routine optimization.

C. It is not obvious to optimize a result-effective parameter unrecognized in the art.

The Examiner has previously rejected claim 95 and now rejects claims 74-76, 78, 80, 82-84, 94 as being unpatentable over Lipford in view of the teachings of Kensil and further by routine optimization. Appellants have argued that it cannot be obvious to optimize the sterol:saponin ratio of the compositions disclosed by the cited references, because this ratio was not recognized in the art as a result-effective parameter (See MPEP 2144.05.IIB Optimization of Ranges - Only Result Effective Variables can be Optimized.) The Examiner has answered that "Kensil and Lipford do suggest a result-effective basis for such optimization . . . by teaching the hemolytic activity of saponins and indicating that this activity arises from the incalation of the saponin in cholesterol containing membranes." (Lipford page 78.) According to the Examiner, "these teachings suggest that the hemolytic activity of the saponins in the compositions of the references is counteracted by the presence of the cholesterol in the cholesterol/saponin formulations described." (Answer page 15 first paragraph.) The Examiner submits that these suggested teachings would further suggest to a person of ordinary skill in the art to optimize the saponin to sterol ratio, in order to reduce the hemolytic activity.

Appellants maintain the traversal of the rejection. The alleged teaching that the Examiner is relying on is simply not to be found in the art. Kensil teaches that purified saponins can vary in their hemolytic activity. There is no suggestion in Kensil to try varying or counteracting the hemolytic activity of QS21, and no suggestion to try to do so using cholesterol. Lipford teaches only that the hemolytic qualities of Quil A can be explained by its ability to intercalate with

cholesterol-containing membranes and that this membrane-fusogenic quality is beneficial, aiding in the transport of antigen into the cytosolic compartment. (Lipford page 78.) There is no suggestion in Lipford that a person of ordinary skill in the art would want to counteract this hemolytic quality of Quil A and no suggestions that the hemolytic qualities of Quil A in Lipford's compositions are counteracted by the presence of the cholesterol in the Lipford formulations.

Appellants have shown that the claimed ratio was not recognized in the art as a result-effective variable and that the cited references teach away from the claimed optimization, or at the very least fail to disclose a need to optimize the parameters in the manner claimed by the Appellants. Appellants submit that, as in the Whelan case cited in the Answer, "the Examiner has not persuasively explained why a person of ordinary skill in the art would have had a reason to modify the compositions taught by [the cited references] in a way that would result in the compositions defined by the claims on appeal." *Ex parte Whalen II.* Appeal 2007-4423 p.16 BPAI (2008.)"

Respectfully submitted,

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CLAIMS APPENDIX

1-73. (Canceled)

74. (Previously presented) A composition comprising: 1) an antigen; 2) a saponin which is substantially pure QS21; 3) a sterol that is present in excess by weight with respect to the saponin and wherein the ratio of saponin to sterol does not exceed 1:100 w/w.

75. (Previously presented) The composition of Claim 74 wherein the weight:weight ratio of QS21 to sterol is 1:2 to 1:100.

76. (Previously presented) The composition of Claim 75 wherein the sterol is cholesterol.

77. (Previously presented) The composition of Claim 74 which further comprises a derivative of an enterobacterial lipopolysaccharide.

78. (Previously presented) The composition of Claim 74 which further comprises a metal particle salt carrier selected from the group consisting of phosphate and hydroxide salts of aluminum, zinc, calcium, cerium, chromium, iron, and beryllium.

79. (Previously presented) The composition of Claim 76 which further comprises a 3-O-deacylated monophosphoryl lipid A.

80. (Previously presented) The composition of Claim 76 which further comprises aluminum hydroxide or aluminum phosphate.

81. (Previously presented) The composition of Claim 76 which further comprises a 3-O-deacylated monophosphoryl lipid A and aluminum hydroxide or aluminum phosphate.

82 (Previously presented) The composition of Claim 79 wherein the saponin is at least 98% pure QS21.

83. (Previously presented) The composition of Claim 74 wherein the sterol and the QS21 are in a vesicle-like structure.

84. (Previously presented) The composition of Claim 74 wherein the antigen is derived from Human Immunodeficiency virus, Feline Immunodeficiency virus, Varicella Zoster virus, Herpes Simplex virus type 1, Herpes Simplex virus type 2, Human cytomegalovirus, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis E, Respiratory Syncytial virus, Human Papilloma virus, Influenza virus, Haemophilus Influenza B, Meningitis virus, Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Plasmodium, or Toxoplasma.

85-93 (Canceled)

94. (Previously presented) The composition of 83 wherein the sterol is cholesterol and the vesicle like structures are unilamellar liposomes.

95. (Previously presented) The composition of claim 74 wherein the ratio of saponin to sterol is between above 1:1 and about 1:5 w/w.

96. (Canceled)